

Preventive and therapeutic potential of ascorbic acid in neurodegenerative diseases

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Summary

In this review, we summarize the involvement of ascorbic acid in neurodegenerative diseases by presenting available evidence on the behavioral and biochemical effects of this compound in animal models of neurodegeneration as well as the use of ascorbic acid as a therapeutic approach to alleviate neurodegenerative progression in clinical studies. Ascorbate, a reduced form of vitamin C, has gained interest for its multiple functions and mechanisms of action, contributing to the homeostasis of normal tissues and organs as well as to tissue regeneration. In the brain, ascorbate exerts neuromodulatory functions and scavenges reactive oxygen species generated during synaptic activity and neuronal metabolism. These are important properties as redox imbalance and abnormal protein aggregation constitute central mechanisms implicated in the pathogenesis of neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, multiple sclerosis, and amyotrophic lateral sclerosis. Indeed, several studies have indicated an association between low serum ascorbate concentrations and neurodegeneration. Moreover, ascorbic acid is a suitable candidate for supplying either antioxidant defense or modulation of neuronal and astrocytic metabolism under neurodegenerative conditions. Ascorbic acid acts mainly by decreasing oxidative stress and reducing the formation of protein aggregates, which may contribute to the reduction of cognitive and/or motor impairments observed in neurodegenerative processes. Although several studies support a possible role of ascorbic acid administration against neurodegeneration, more researches are essential to substantiate the existing results and accelerate the knowledge in this field.

KEYWORDS

ascorbic acid, central nervous system, neurodegeneration, neuromodulation

1 | INTRODUCTION

Neurodegenerative diseases are a range of conditions that are characterized by the progressive functional and structural degeneration of the central or peripheral nervous system. They comprise a set of over 600 diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, multiple sclerosis, and amyotrophic lateral sclerosis. Excitotoxicity, the specific type of toxicity mediated by glutamate, is a hallmark of neurodegenerative diseases. Neuronal excitotoxicity is associated with calcium overload and mitochondrial dysfunction,

which may result in energy supply deficiency as well as generation of high levels of reactive oxygen species such as superoxide anion, hydroxyl radical, and hydrogen peroxide, crucial contributors to neuronal death. This common feature in different neurodegenerative diseases suggests that disorders with distinct genetic etiologies may share excitotoxicity and its consequences as a common pathogenic pathway.¹

The pathogenesis of neurodegenerative diseases also involves atypical accumulation of misfolded proteins and aggregation of disease-specific proteins, which are deposited in intracellular inclusions or extracellular aggregates. Commonly implicated proteins

include tau and amyloid- β (A β) in Alzheimer's disease, α -synuclein in Parkinson's disease, and huntingtin in Huntington's disease. Protein aggregates are also observed in multiple sclerosis² and amyotrophic lateral sclerosis,³ although further studies are required to confirm the role of soluble aggregates in these diseases.

Ascorbic acid, a water-soluble vitamin essential for several physiological processes in the human body, is concentrated in the brain and is involved in the central nervous system (CNS) homeostasis. Figure 1 shows ascorbate uptake and metabolism in the CNS. Ascorbate enters the CNS by slow transport from plasma to the cerebrospinal fluid across the choroid plexus epithelium, via type 2 sodium-dependent transporters (SVCT2). If considerable amounts of dehydroascorbate (oxidized form of ascorbate) are present in the blood, it can rapidly enter the CNS via glucose transporters (GLUT1) present in the blood-brain barrier endothelium. Once in the cerebrospinal fluid, ascorbate or dehydroascorbate enters the neurons through SVCT2 or GLUT1, respectively; dehydroascorbate can be reduced to ascorbate or released by GLUT1.

Ascorbate serves as a one-electron donor, producing the ascorbate free radical, which is reduced back to ascorbate within cells by NADH- and NADPH-dependent reductases. Different from neurons, ascorbate uptake in glial cells does not seem to involve SVCT2; they obtain ascorbate by the reduction in dehydroascorbate, uptaken by GLUT1.⁴

Neuronal and glial cells are very sensitive to oxidative stress and neurons appear to be particularly sensitive to ascorbate deficiency; therefore, ascorbate recycling by astrocytes and neuronal uptake through SVCT2 transporters are important mechanisms in re-establishing or maintaining redox homeostasis under oxidative conditions.⁵ Notably, deregulation of cellular redox balance and inflammatory signaling has become increasingly discussed in modern view of neurodegenerative diseases mechanisms,⁶⁻¹⁰ raising the hypothesis that ascorbic acid could have therapeutic roles against these diseases.

In addition to its antioxidant effects, it has been suggested that ascorbate exerts important neuromodulatory functions in the

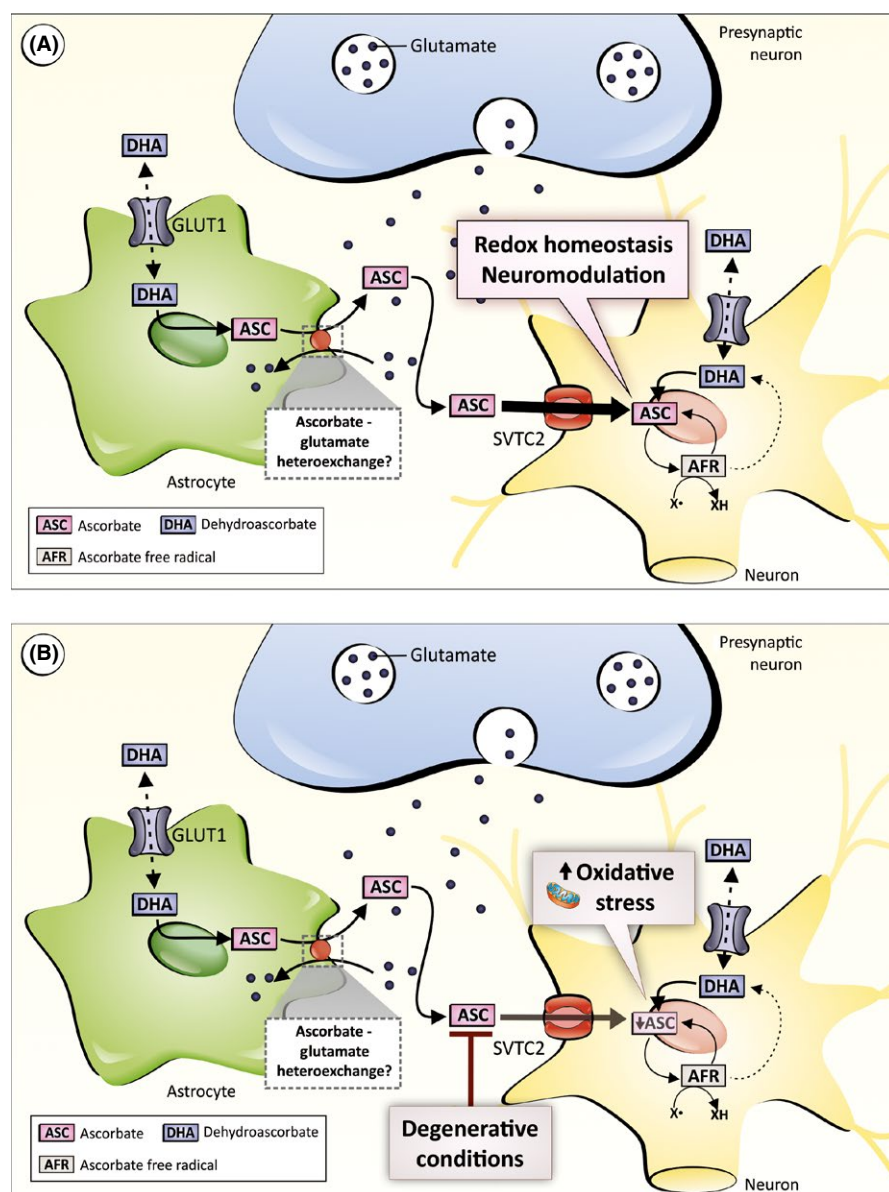


FIGURE 1 A, Ascorbate or dehydroascorbate enters the neurons through SVCT2 or GLUT1, respectively, being the transport via SVCT2 the primary form of neuronal uptake of this molecule. In the neuronal milieu, dehydroascorbate can be reduced to ascorbate or released back into the extracellular space by GLUT1. Ascorbate serves as a one-electron donor, producing the ascorbate free radical, which is reduced back to ascorbate within cells. Glial cells obtain dehydroascorbate (uptaken by GLUT1), which is subsequently reduced to ascorbate.⁴ Ascorbate transport from astrocytes to the extracellular environment has been linked to glutamate uptake in a process termed "ascorbate-glutamate heteroexchange." Under physiological conditions, ascorbate exerts antioxidant and neuromodulatory functions in the CNS. B, Under neurodegenerative conditions, there is a failure in neuronal ascorbate uptake, leading to ascorbate deficiency in brain areas affected by neurodegeneration, worsening the redox imbalance, metabolic failure, and tissue damage in these areas

CNS. Its functional role in modulating glutamatergic neurotransmission^{11–13} is of particular interest, as degenerative processes are associated with neurotoxic effects produced by excessive glutamate availability in the synaptic cleft, due to excessive release or impaired uptake of this neurotransmitter.¹⁴ The effects of ascorbate on the glutamatergic system could be due to redox modulation of the NMDA receptor itself by ascorbate,¹³ or to direct scavenging of reactive oxygen species generated by receptor activation. Moreover, ascorbate transport from astrocytes to the extracellular environment has been linked to glutamate uptake in a process termed “ascorbate-glutamate heteroexchange,”¹² which decreases extracellular glutamate levels and, in turn, reduces excitotoxicity and pro-oxidative damage.

Outstandingly, some studies have suggested a failure in neuronal ascorbate uptake in inflammatory and neurodegenerative events.¹⁵ The concept that intracellular ascorbate is critical for protection against oxidative stress and neuromodulation leads to the assumption that ascorbate deficiency in brain areas affected by neurodegeneration or inflammation will worsen redox imbalance, metabolic failure, and tissue damage.

Considering the involvement of ascorbate in the regulation of the CNS function, we present clinical and nonclinical studies that have investigated the association of this compound with neurodegenerative diseases. We focus on behavioral and biochemical effects of ascorbic acid administration in animal models that are suitable for this area of research, as well as clinical studies that target the potential therapeutic use of ascorbic acid.

2 | ROLE OF ASCORBIC ACID IN NEURODEGENERATIVE DISEASES

2.1 | Alzheimer's disease

Alzheimer's disease, the most common form of neurodegenerative dementia, is a multifaceted disorder whose progression depends on several genetic, environmental, and physiological factors.¹⁶ The potential beneficial effects of ascorbic acid have been investigated in animal models of Alzheimer's disease with encouraging results. Using a mouse model, Murakami and colleagues¹⁷ demonstrated that a 6-month treatment with ascorbic acid restored behavioral deficits and reduced the formation of A β oligomers. This attenuation of A β oligomerization was accompanied by decreased brain oxidative damage and reduced ratio of soluble A β 42 to A β 40, a characteristic indicator of disease progression. In the same study, the authors showed that ascorbic acid restored the declined brain synaptophysin and phosphorylation of Tau at Ser39. In agreement with these findings, the treatment with ascorbic acid reduced oxidative stress markers and proinflammatory cytokines in rats that received hippocampal (CA1) injection of fibrillar A β .¹⁸ Data from another study revealed that ascorbic acid completely abolished the increase in intracellular calcium and cell death induced by A β in PC12 cells.¹⁹

Sil et al²⁰ have investigated the role of ascorbic acid on the neuroinflammation-mediated neurodegeneration and memory

impairments in colchicine-induced rat model of Alzheimer's disease. The authors reported that administration of ascorbic acid (200 and 400 mg/kg for 21 days) resulted in recovery of memory impairments, with prevention of neurodegeneration and neuroinflammation in the hippocampus of colchicine-induced Alzheimer's disease rats. Moreover, inflammation parameters (TNF- α , IL-1 β , reactive oxygen species, and nitrite levels) in the serum of colchicine-induced Alzheimer's disease rats were also recovered at 200 and 400 mg/kg dose of ascorbic acid. Interestingly, colchicine-induced Alzheimer's disease rats treated with 600 mg/kg of ascorbic acid showed greater memory impairment, neurodegeneration, and neuroinflammation in the hippocampus paralleled with alteration of peripheral immune responses in comparison with colchicine-treated rats that did not receive ascorbic acid. Therefore, it seems that ascorbic acid at lower doses shows antioxidant effect and at higher dose induces pro-oxidant/neurotoxic effects in colchicine-induced Alzheimer's disease model.

Very recently, Olajide et al²¹ examined the effects of ascorbic acid on behavioral and cortical and hippocampal neurochemical changes elicited by repeated administration of aluminum chloride (AlCl₃), a model of Alzheimer's disease, in rats. A 15-day treatment with ascorbic acid (100 mg/kg daily) significantly decreased behavioral deficits in rats through inhibition of molecular and cellular stressor proteins activated by AlCl₃. The main mechanisms underlying ascorbic acid therapeutic effects seem to be related to its ability to scavenge free radicals, prevent membrane lipid peroxidation, modulate neuronal bioenergetics, and inhibit acetylcholinesterase and through its antiproteolytic properties.

An interesting hypothesis raised by Dixit et al²² is that decreased brain ascorbate could induce oxidative stress at an early age and accelerate the development of pathological changes such as A β deposition and the consequent cognitive deficits. This hypothesis came from data showing that mice with a lifelong decrease in ascorbic acid presented changes from a much earlier stage of amyloid accumulation, at 6 months. Furthermore, ascorbic acid administration (1 mmol/L) suppressed reactivity of the A β A11, an antibody that recognizes a specific conformation of toxic, prefibrillar A β oligomers, in Tg2576 fibroblasts.²³

Clinical studies have also investigated the relationship between Alzheimer's disease and ascorbic acid intake or plasma levels of ascorbate, but results do not allow us to come to definitive conclusions. Riviere et al²⁴ found that plasma ascorbate levels are lower in Alzheimer's disease individuals in proportion to the degree of cognitive impairment, despite adequate ascorbic acid intake. Morris et al²⁵ investigated the relation between the use of vitamins E and ascorbic acid and the risk of incident Alzheimer's disease in a prospective study with a sample of 633 people aged 65 years and older. It was shown that none of the individuals supplemented with ascorbic acid had Alzheimer's disease over the follow-up period (mean of 4 years). Basambombo et al²⁶ recently evaluated whether the use of vitamins E and C supplements is associated with reduced risks of cognitive impairment, dementia, Alzheimer's disease, or all-cause dementia in a sample of 5269 persons ≥ 65 years old. Compared with those not taking vitamin supplements, individuals using vitamin E and/or

vitamin C supplements presented reduced risk of cognitive decline and Alzheimer's disease. In line with these findings, a study with over 5000 participants revealed that high intake of ascorbic acid was associated with lower risk of Alzheimer's disease after a mean follow-up period of 6 years.²⁷ Conversely, another prospective study conducted with a sample of 815 community-dwelling residents 65 years and older and free of Alzheimer's disease at baseline found that intake of ascorbic acid was not significantly associated with risk of this disease during the follow-up period (mean of 3.9 years).²⁸ Finally, the combined supplementation with vitamin E and ascorbic acid was reported to be associated with reduced prevalence and incidence of Alzheimer's disease in a cross-sectional and prospective study with individuals 65 years or older. However, ascorbic acid alone did not reduce the risk for this disease.²⁹ The main findings on the association between ascorbic acid and Alzheimer's disease are shown in Table 1.

2.2 | Parkinson's disease

The discovery that α -synuclein, the main component of the pathological protein aggregates known as Lewy bodies, is genetically and neuropathologically linked to Parkinson's disease has dramatically evolved the knowledge regarding the pathogenesis of this disease. Studies have shown a significant effect of ascorbate on α -synuclein. For instance, ascorbate may directly reduce α -synuclein-Cu²⁺ (which accelerates the formation of toxic aggregates) to α -synuclein-Cu⁺,

setting up a redox cycle in which O₂ is reduced to H₂O₂ and cellular redox species are continuously exhausted.³⁰ Moreover, ascorbic acid reduces the formation of α -synuclein by preventing the excessive ROS formation in *Saccharomyces cerevisiae* cells.³¹ Importantly, overexpressed α -synuclein is believed to increase the sensitivity of dopaminergic neurons to oxidative damage, causing mitochondrial dysfunction,³² alterations that may be related to the possible mechanisms by which ascorbic acid may be helpful for the management of Parkinson's disease.

In patients with severe Parkinson's disease, lymphocyte ascorbate levels were reported to be lower as compared to patients at less severe stages, suggesting that lymphocyte ascorbate levels could be a potential biomarker for progression of the disease.³³ However, Fernandez-Calle et al³⁴ found that patients with Parkinson's disease and healthy individuals have similar serum levels of ascorbic acid. Moreover, serum levels of this vitamin did not correlate with age, or age at onset and duration of Parkinson's disease. Another study showed that ascorbic acid levels in leukocytes were higher in patients with Parkinson's disease as compared to age-matched control subjects with equivalent disability resulting from non-neurological diseases.³⁵

The association between the intake of antioxidant vitamins, including ascorbic acid, and Parkinson's disease risk was prospectively examined in two large cohort studies.³⁶ It was revealed that dietary ascorbic acid intake was significantly associated with reduced Parkinson's disease risk; however, this result was not significant in

TABLE 1 Clinical studies that investigated the relation between ascorbic acid and Alzheimer's disease

Reference	Study design	Sample	Measurement/intervention	Main findings
24	Case-control	Patients with Alzheimer's disease divided in 4 groups: severe Alzheimer (N = 20); moderate Alzheimer (N = 24); hospitalized Alzheimer (N = 9); control group (N = 19)	Comparison of ascorbate plasma levels and assessment of ascorbic acid intake and nutritional status	Plasma ascorbate is ↓ in Alzheimer's disease in proportion to the degree of cognitive impairment, an effect not explained by lower ascorbic acid intake
25	Prospective cohort study	633 disease-free persons 65 y and older	The relation between use of ascorbic acid and incident Alzheimer's disease	None of the 23 ascorbic acid users had Alzheimer's disease compared with 3.3 predicted based on the crude observed incidence among nonusers and 3.2 predicted adjusted for age, sex, education, and follow-up interval (4.3 y)
26	Prospective cohort study	5269 individuals ≥65 y old, free of dementia at baseline	The relation between vitamin E and C supplements and risks of cognitive impairment, not dementia, Alzheimer's disease, or all-cause dementia	The use of vitamin E and C supplements was associated with decreased risks of all-cause dementia and Alzheimer's disease
27	Prospective cohort study	5395 participants aged at least 55 y, free of dementia at baseline	The relation between dietary intake of antioxidants and risk of Alzheimer's disease	↑ intake of ascorbic acid was associated with ↓ risk of Alzheimer's disease
28	Prospective cohort study	815 community-dwelling residents 65 y and older, free of Alzheimer's disease at baseline	Association between intake of ascorbic acid and incident Alzheimer's disease	Intake of ascorbic acid was not significantly associated with risk of Alzheimer's disease
29	Cross-sectional and prospective study	5092 elderly residents free of Alzheimer's disease at baseline	Relationship between antioxidant supplement use and risk of Alzheimer's disease	Use of vitamin E and ascorbic acid supplements in combination is associated with ↓ prevalence and incidence of Alzheimer's disease

a 4-year lag analysis. These findings suggest that intake of ascorbic acid, as well as vitamin E and carotenoids, at least at the levels consumed in these cohorts, does not substantially affect the risk of Parkinson's disease. Using data from a multicenter hospital-based case-control study, Miyake et al³⁷ also investigated the relationship between dietary intake of selected antioxidant vitamins, vegetables, and fruits and the risk of Parkinson's disease in Japan. The authors found no substantial associations between intake of vitamin C, α -carotene, cryptoxanthin, green and yellow vegetables, other vegetables, or fruits and the risk of Parkinson's disease. In agreement with these findings, in two large cohorts of men and women who completed detailed and validated semiquantitative food frequency questionnaires, high ascorbic acid consumption did not reduce the risk of Parkinson's disease.³⁸

Regarding clinical trials evaluating the effect of ascorbic acid in patients with Parkinson's disease, Fahn³⁹ showed that patients with early Parkinson's disease using high dosages of tocopherol and ascorbic acid in combination had a 2.5 years of delay in the time to initiation of levodopa therapy, suggesting that the combined administration of these antioxidants may slow the progression of this disease. However, these results do not allow us to detect the individual contribution of ascorbic acid for this effect. In a double-blind crossover investigation, ascorbic acid produced a modest improvement in functional performance of patients with Parkinson's disease who experienced on-off effects, but no significant alteration was found in the pattern of on-off effects, severity of parkinsonism/dyskinesia, or self-assessment ratings.⁴⁰ Table 2 summarizes results from studies investigating ascorbic acid and Parkinson's disease association.

2.3 | Huntington's disease

Huntington's disease is a genetic neurodegenerative disorder characterized by the progressive loss of neurons, mainly in the striatum, which leads to movement abnormalities and cognitive deficits.

Preclinical studies suggest that besides being associated with ascorbic acid deficiency, Huntington's disease is linked to a deficit of ascorbic acid release into striatal extracellular fluid that either directly or indirectly affects glutamate release by cortical afferents.⁴¹ Interestingly, Rebec et al⁴² showed that a 3-day injection of sodium ascorbate (300 mg/kg) returned the level of striatal extracellular ascorbate in R6/2 mice (a widely used mouse model of Huntington's disease) to that of wild-type controls, suggesting a role for ascorbate in regulating neuronal function in Huntington's disease striatum. Acuña et al¹⁵ proposed that before behavioral symptoms of Huntington's disease, astrocytes do not release ascorbate efficiently, suggesting a disturbed ascorbate homeostasis in the presymptomatic stages of Huntington's-like disease in mice. The same study revealed that an over-supplementation of R6/2 slices with exogenous ascorbic acid is enough to produce an adequate ascorbate uptake, an effect that is abolished by inhibition of ascorbic acid uptake (by anti-SVCT2 antibody). Moreover, during symptomatic stages of Huntington's disease in mice, exogenous ascorbic acid is not able to induce the ascorbate transporter SVCT2 translocation to the plasma membrane, a process that depends on huntingtin. Considering the importance of ascorbate homeostasis in Huntington's disease, new studies are required to investigate this compound as an adjunctive therapy in this pathology.

2.4 | Multiple sclerosis and amyotrophic lateral sclerosis

Multiple sclerosis is a chronic inflammatory disease of the CNS associated with demyelination, neurodegeneration, and increased oxidative stress. Besides its well-known role as a scavenger of free radicals,⁴³ ascorbate contributes for the synthesis of collagen, which is associated with myelin formation.⁴ Moreover, it is essential to promote Schwann cell myelin formation, as elegantly demonstrated by Eldridge et al.⁴⁴ These properties of ascorbate have raised the hypotheses that

TABLE 2 Findings on ascorbic acid and Parkinson's disease association

Reference	Study design	Sample	Measurement/intervention	Main findings
36	Prospective cohort study	1036 Parkinson's disease cases	Associations between intakes of ascorbic acid, vitamin E, and carotenoids and risk of Parkinson's disease	Dietary ascorbic acid intake was associated with reduced Parkinson's disease risk, a result not significant in a 4-y lag analysis
37	Case-control	249 patients within 6 y of onset of Parkinson's disease and 368 healthy controls	Associations between intakes of ascorbic acid and risk of Parkinson's disease	Ascorbic acid consumption did not reduce the risk of Parkinson's disease
38	Prospective cohort study	76 890 women who were followed for 14 y and 47 331 men who were followed for 12 y	Associations between intakes of ascorbic acid or vitamin supplements and risk of Parkinson's disease	Neither intake of total ascorbic acid or use of ascorbic acid supplements or multivitamins was significantly associated with risk of Parkinson's disease
39	Open trial	15 patients with early Parkinson's disease	Association between the use of high dosages of tocopherol and ascorbate and the time when levodopa became necessary	The time when levodopa became necessary was extended by 2.5 y in the group taking tocopherol + ascorbate compared with another group of patients not taking antioxidants

this compound could be useful for the prevention and/or treatment of multiple sclerosis.

Babri et al⁴⁵ investigated the effect of intrahippocampal injection of ascorbic acid and progesterone, alone or in combination, on passive avoidance learning in a rat model of multiple sclerosis induced by ethidium bromide. The authors reported that ascorbic acid improved memory for passive avoidance learning, but progesterone alone or in combination with ascorbic acid had no improving

effects on memory. The effects of ascorbic acid in this model may be dependent on its modulatory role on neurotransmitter systems such as cholinergic^{46,47} and serotonergic⁴⁷ systems. In addition, the activity of the enzyme acetyl cholinesterase, which has an essential role in learning and memory processes, was reported to be modulated by ascorbic acid.⁴⁸ Finally, the antioxidant properties of ascorbic acid^{49,50} may also contribute for its effect in models of multiple sclerosis.

TABLE 3 Epidemiological studies that investigated the relation between ascorbic acid and multiple sclerosis/amyotrophic lateral sclerosis

Reference	Study design	Sample	Measurement/intervention	Main findings
51	Cross-sectional	24 patients with multiple sclerosis and 24 healthy sex- and age-matched control	Assessment of serum levels of ascorbate and lipid peroxidation	Decreased ascorbate in serum of patients with multiple sclerosis during an attack, an effect associated with increased lipid peroxidation products
52	Case-control	197 incident cases of multiple sclerosis and 202 matched controls	Association between intake of ascorbic acid and risk of multiple sclerosis	Higher intakes of ascorbic acid were negatively associated with the risk of multiple sclerosis
53	Prospective cohort study	Cohort 1: 81 683 women aged 38-63 y. Cohort 2: 95 056 women aged 27-44 y in	Association between intake of dietary ascorbic acid and the risk of multiple sclerosis	No associations between intakes of fruits and vegetables, use of ascorbic acid, or multivitamin supplements and the risk of multiple sclerosis
61	Case-control	153 patients with amyotrophic lateral sclerosis aged 18-81 and 306 gender- and age-matched controls	Association between intake of ascorbic acid and risk of amyotrophic lateral sclerosis	Dietary ascorbic acid intake was not associated with amyotrophic lateral sclerosis risk

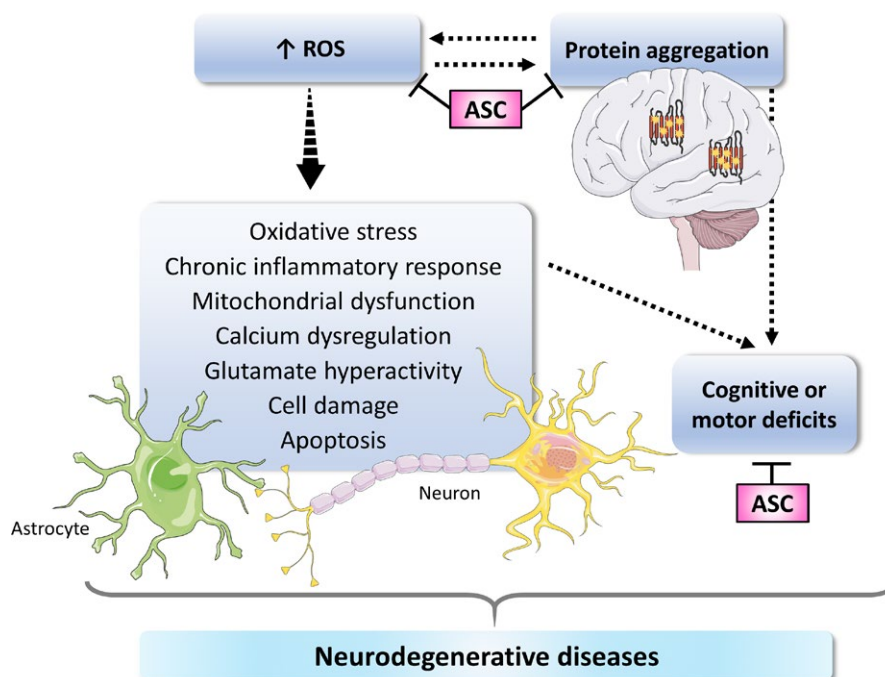


FIGURE 2 Neurodegenerative diseases are associated with increased reactive oxygen species (ROS) in the brain. The large amounts of ROS and impaired antioxidant defenses observed in these pathologies lead to neuronal oxidative stress, chronic inflammatory response, mitochondrial dysfunction, calcium dysregulation, glutamate hyperactivity, cell damage, and apoptosis. Most importantly, excessive ROS participates in events associated with protein aggregation and cognitive dysfunction through damaging effects on proteins, lipids, and DNA. Clinical and nonclinical studies have indicated that ascorbate (ASC) has neuroprotective effects mainly by reducing oxidative stress and formation of protein aggregates, which may contribute to the reduction of cognitive decline or motor deficits observed in these diseases

Epidemiologic data associating ingestion of ascorbic acid to risk of multiple sclerosis are sparse and controversial. The serum levels of ascorbate were evaluated in 24 patients with multiple sclerosis and 24 healthy sex- and age-matched individuals as control. It was observed that the levels of ascorbate, as well as other antioxidant vitamins (alpha tocopherol, beta-carotene, and retinol) were decreased in the serum of patients with multiple sclerosis during an attack, an effect associated with increased oxidative burden, as reflected by increased lipid peroxidation products.⁵¹ Another case-control study reported that higher intakes of ascorbic acid were negatively associated with the risk of multiple sclerosis.⁵² Zhang et al⁵³ prospectively examined the association between intake of dietary ascorbic acid, and the risk of multiple sclerosis in two large cohorts of women who completed detailed and validated semiquantitative food frequency questionnaires. The authors found no associations between intakes of fruits and vegetables, use of ascorbic acid, or multivitamin supplements and the risk of multiple sclerosis. In agreement with this finding, intakes of fruits and vegetables, which are rich in ascorbic acid, were not associated with the risk of multiple sclerosis in other studies.⁵⁴⁻⁵⁶

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease of spinal cord motor neurons. It leads to atrophy of skeletal muscles, paralysis, and rapid progression to death. As copper toxicity in motor neurons, free radical accumulation, and oxidative stress have been proposed as contributors to the progression of amyotrophic lateral sclerosis,^{57,58} the neuroprotective effect of the treatment with trientine (a chelating agent for copper) and ascorbate was examined in familial amyotrophic lateral sclerosis transgenic mice. It was reported that the onset of neurological signs and the time to reach total paralysis in the group treated with trientine plus ascorbic acid was significantly delayed compared with that in the control group.⁵⁹ In another study using the same model, mice administered with trientine or ascorbate alone before the onset of the disease survived significantly longer than the controls. The combined treatment with a high dose of trientine and ascorbate initiated before the onset of the disease extended survival and improved motor function. Interestingly, none of the treatments administered after the onset of the disease prolonged survival, suggesting that better outcomes may be predictable by the administration of these agents at the preonset stage of the disease.⁶⁰

As far as we know, there is only one study examining the association between dietary intake of ascorbic acid and the risk of amyotrophic lateral sclerosis. Using a self-administered questionnaire, Okamoto et al⁶¹ investigated the association between dietary intake of fruits, vegetables, and antioxidants and the risk of amyotrophic lateral sclerosis in Japan. In this study, no statistically significant dose-response relationship was observed between intake of ascorbic acid and the risk of amyotrophic lateral sclerosis, but higher intake of food rich in antioxidants such as fruits and vegetables conferred protection against the development of this disease.

Table 3 summarizes results from epidemiological studies that investigated the association between ascorbic acid and multiple sclerosis/amyotrophic lateral sclerosis. Undoubtedly, there is insufficient evidence of this association until now.

3 | CONCLUSIONS

Studies investigating the effects of ascorbic acid in neurodegenerative diseases are still in their infancy, and the association between this neuromodulator and the diseases discussed here remains to be explored. As summarized in Figure 2, the current knowledge on the effects of ascorbic acid in neurodegenerative processes suggests that this compound acts mainly by decreasing oxidative stress and reducing the formation of protein aggregates, which may contribute to the reduction of cognitive and/or motor impairments observed in these neuropathologies. The available epidemiological studies in this regard are in general poorly designed, and underpowered, with low sample and of short duration. Although ours and other recently published reviews^{62,63} have shown a possible beneficial effect of ascorbic acid administration against neurodegeneration, more researches are clearly required to substantiate the existing results and accelerate the knowledge in this field.

CONFLICT OF INTEREST

The authors declare that no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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REFERENCES

1. Trippier PC, Jansen Labby K, Hawker DD, Mataka JJ, Silverman RB. Target- and mechanism-based therapeutics for neurodegenerative diseases: strength in numbers. *J Med Chem*. 2013;56:3121-3147.
2. David MA, Tayebi M. Detection of protein aggregates in brain and cerebrospinal fluid derived from multiple sclerosis patients. *Front Neurol*. 2014;5:251.
3. Blokhuis AM, Groen EJ, Koppers M, van den Berg LH, Pasterkamp RJ. Protein aggregation in amyotrophic lateral sclerosis. *Acta Neuropathol*. 2013;125:777-794.
4. Harrison FE, May JM. Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. *Free Radic Biol Med*. 2009;46:719-730.
5. May JM, Huang J, Qu ZC. Macrophage uptake and recycling of ascorbic acid: response to activation by lipopolysaccharide. *Free Radic Biol Med*. 2005;39:1449-1459.
6. Aguiar CC, Almeida AB, Araujo PV, et al. Oxidative stress and epilepsy: literature review. *Oxid Med Cell Longev*. 2012;2012:795259.
7. Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. *Oxid Med Cell Longev*. 2012;2012:428010.
8. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:676-692.
9. Sorolla MA, Rodriguez-Colman MJ, Vall-Illaura N, Tamarit J, Ros J, Cabiscol E. Protein oxidation in Huntington disease. *BioFactors*. 2012;38:173-185.

10. Yao JK, Keshavan MS. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. *Antioxid Redox Signal*. 2011;15:2011-2035.
11. Moretti M, Freitas AE, Budni J, Fernandes SC, Balen G, Rodrigues AL. Involvement of nitric oxide-cGMP pathway in the antidepressant-like effect of ascorbic acid in the tail suspension test. *Behav Brain Res*. 2011;225:328-333.
12. Rebec GV, Pierce RC. A vitamin as neuromodulator – ascorbate release into the extracellular fluid of the brain regulates dopaminergic and glutamatergic transmission. *Prog Neurobiol*. 1994;43:537-565.
13. Majewska MD, Bell JA, London ED. Regulation of the NMDA receptor by redox phenomena: inhibitory role of ascorbate. *Brain Res*. 1990;537:328-332.
14. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. *Science*. 1993;262:689-695.
15. Acuna AI, Esparza M, Kramm C, et al. A failure in energy metabolism and antioxidant uptake precede symptoms of Huntington's disease in mice. *Nat Commun*. 2013;4:2917.
16. Bagyinszky E, Giau VV, Shim K, Suk K, An SSA, Kim S. Role of inflammatory molecules in the Alzheimer's disease progression and diagnosis. *J Neurol Sci*. 2017;376:242-254.
17. Murakami K, Murata N, Ozawa Y, et al. Vitamin C restores behavioral deficits and amyloid-beta oligomerization without affecting plaque formation in a mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2011;26:7-18.
18. Rosales-Corral S, Tan DX, Reiter RJ, et al. Orally administered melatonin reduces oxidative stress and proinflammatory cytokines induced by amyloid-beta peptide in rat brain: a comparative, in vivo study versus vitamin C and E. *J Pineal Res*. 2003;35:80-84.
19. Yallampalli S, Micci MA, Tagliatalata G. Ascorbic acid prevents beta-amyloid-induced intracellular calcium increase and cell death in PC12 cells. *Neurosci Lett*. 1998;251:105-108.
20. Sil S, Ghosh T, Gupta P, Ghosh R, Kabir SN, Roy A. Dual role of vitamin C on the neuroinflammation mediated neurodegeneration and memory impairments in Colchicine induced rat model of Alzheimer Disease. *J Mol Neurosci*. 2016;60:421-435.
21. Olajide OJ, Yawson EO, Gbadamosi IT, et al. Ascorbic acid ameliorates behavioural deficits and neuropathological alterations in rat model of Alzheimer's disease. *Environ Toxicol Pharmacol*. 2017;50:200-211.
22. Dixit S, Bernardo A, Walker JM, et al. Vitamin C deficiency in the brain impairs cognition, increases amyloid accumulation and deposition, and oxidative stress in APP/PSEN1 and normally aging mice. *ACS Chem Neurosci*. 2015;6:570-581.
23. Cheng F, Cappai R, Ciccotosto GD, et al. Suppression of amyloid beta A11 antibody immunoreactivity by vitamin C: possible role of heparan sulfate oligosaccharides derived from glypican-1 by ascorbate-induced, nitric oxide (NO)-catalyzed degradation. *J Biol Chem*. 2011;286:27559-27572.
24. Riviere S, Birlouez-Aragon I, Nourhashemi F, Vellas B. Low plasma vitamin C in Alzheimer patients despite an adequate diet. *Int J Geriatr Psychiatry*. 1998;13:749-754.
25. Morris MC, Beckett LA, Scherr PA, et al. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1998;12:121-126.
26. Basambombo LL, Carmichael PH, Cote S, Laurin D. Use of vitamin E and C supplements for the prevention of cognitive decline. *Ann Pharmacother*. 2017;51:118-124.
27. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA*. 2002;287:3223-3229.
28. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA*. 2002;287:3230-3237.
29. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol*. 2004;61:82-88.
30. Wang C, Liu L, Zhang L, Peng Y, Zhou F. Redox reactions of the alpha-synuclein-Cu(2+) complex and their effects on neuronal cell viability. *Biochemistry*. 2010;49:8134-8142.
31. Fernandes JT, Tenreiro S, Gameiro A, Chu V, Outeiro TF, Conde JP. Modulation of alpha-synuclein toxicity in yeast using a novel microfluidic-based gradient generator. *Lab Chip*. 2014;14:3949-3957.
32. Stefanis L. alpha-synuclein in Parkinson's disease. *Cold Spring Harb Perspect Med*. 2012;2:a009399.
33. Ide K, Yamada H, Umegaki K, et al. Lymphocyte vitamin C levels as potential biomarker for progression of Parkinson's disease. *Nutrition*. 2015;31:406-408.
34. Fernandez-Calle P, Jimenez-Jimenez FJ, Molina JA, et al. Serum levels of ascorbic acid (vitamin C) in patients with Parkinson's disease. *J Neurol Sci*. 1993;118:25-28.
35. King D, Playfer JR, Roberts NB. Concentrations of vitamins A, C and E in elderly patients with Parkinson's disease. *Postgrad Med J*. 1992;68:634-637.
36. Hughes KC, Gao X, Kim IY, et al. Intake of antioxidant vitamins and risk of Parkinson's disease. *Mov Disord*. 2016;31:1909-1914.
37. Miyake Y, Fukushima W, Tanaka K, et al. Dietary intake of antioxidant vitamins and risk of Parkinson's disease: a case-control study in Japan. *Eur J Neurol*. 2011;18:106-113.
38. Zhang SM, Hernan MA, Chen H, Spiegelman D, Willett WC, Ascherio A. Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. *Neurology*. 2002;59:1161-1169.
39. Fahn S. An open trial of high-dosage antioxidants in early Parkinson's disease. *Am J Clin Nutr*. 1991;53(1 Suppl):380S-382S.
40. Reilly DK, Hershey L, Rivera-Calimlim L, Shoulson I. On-off effects in Parkinson's disease: a controlled investigation of ascorbic acid therapy. *Adv Neurol*. 1983;37:51-60.
41. Rebec GV, Barton SJ, Ennis MD. Dysregulation of ascorbate release in the striatum of behaving mice expressing the Huntington's disease gene. *J Neurosci*. 2002;22:RC202.
42. Rebec GV, Conroy SK, Barton SJ. Hyperactive striatal neurons in symptomatic Huntington R6/2 mice: variations with behavioral state and repeated ascorbate treatment. *Neuroscience*. 2006;137:327-336.
43. Rose RC, Bode AM. Biology of free radical scavengers: an evaluation of ascorbate. *FASEB J*. 1993;7:1135-1142.
44. Eldridge CF, Bunge MB, Bunge RP, Wood PM. Differentiation of axon-related Schwann cells in vitro. I. Ascorbic acid regulates basal lamina assembly and myelin formation. *J Cell Biol*. 1987;105:1023-1034.
45. Babri S, Mehrvash F, Mohaddes G, Hatami H, Mirzaie F. Effect of intrahippocampal administration of vitamin C and progesterone on learning in a model of multiple sclerosis in rats. *Adv Pharm Bull*. 2015;5:83-87.
46. Hasanein P, Shahidi S. Effects of combined treatment with vitamins C and E on passive avoidance learning and memory in diabetic rats. *Neurobiol Learn Mem*. 2010;93:472-478.
47. Lee L, Kang SA, Lee HO, et al. Effect of supplementation of vitamin E and vitamin C on brain acetylcholinesterase activity and neurotransmitter levels in rats treated with scopolamine, an inducer of dementia. *J Nutr Sci Vitaminol (Tokyo)*. 2001;47:323-328.
48. Ambali SF, Idris SB, Onukak C, Shittu M, Ayo JO. Ameliorative effects of vitamin C on short-term sensorimotor and cognitive changes induced by acute chlorpyrifos exposure in Wistar rats. *Toxicol Ind Health*. 2010;26:547-558.
49. Moretti M, Budni J, Dos Santos DB, et al. Protective effects of ascorbic acid on behavior and oxidative status of restraint-stressed mice. *J Mol Neurosci*. 2013;49:68-79.
50. Moretti M, Colla A, de Oliveira Balen G, et al. Ascorbic acid treatment, similarly to fluoxetine, reverses depressive-like behavior and brain oxidative damage induced by chronic unpredictable stress. *J Psychiatr Res*. 2012;46:331-340.

51. Besler HT, Comoglu S, Okcu Z. Serum levels of antioxidant vitamins and lipid peroxidation in multiple sclerosis. *Nutr Neurosci*. 2002;5:215-220.
52. Ghadirian P, Jain M, Ducic S, Shatenstein B, Morisset R. Nutritional factors in the aetiology of multiple sclerosis: a case-control study in Montreal, Canada. *Int J Epidemiol*. 1998;27:845-852.
53. Zhang SM, Hernan MA, Olek MJ, Spiegelman D, Willett WC, Ascherio A. Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. *Neurology*. 2001;57:75-80.
54. Antonovsky A, Leibowitz U, Smith HA, et al. Epidemiologic study of multiple sclerosis in Israel. I. An overall review of methods and findings. *Arch Neurol*. 1965;13:183-193.
55. Berr C, Puel J, Clanet M, Ruidavets JB, Mas JL, Alperovitch A. Risk factors in multiple sclerosis: a population-based case-control study in Hautes-Pyrenees, France. *Acta Neurol Scand*. 1989;80:46-50.
56. Gusev E, Boiko A, Lauer K, Riise T, Deomina T. Environmental risk factors in MS: a case-control study in Moscow. *Acta Neurol Scand*. 1996;94:386-394.
57. Gurney ME, Pu H, Chiu AY, et al. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. *Science*. 1994;264:1772-1775.
58. Shibata N, Nagai R, Uchida K, et al. Morphological evidence for lipid peroxidation and protein glycoxidation in spinal cords from sporadic amyotrophic lateral sclerosis patients. *Brain Res*. 2001;917: 97-104.
59. Nagano S, Ogawa Y, Yanagihara T, Sakoda S. Benefit of a combined treatment with trientine and ascorbate in familial amyotrophic lateral sclerosis model mice. *Neurosci Lett*. 1999;265:159-162.
60. Nagano S, Fujii Y, Yamamoto T, et al. The efficacy of trientine or ascorbate alone compared to that of the combined treatment with these two agents in familial amyotrophic lateral sclerosis model mice. *Exp Neurol*. 2003;179:176-180.
61. Okamoto K, Kihira T, Kobashi G, et al. Fruit and vegetable intake and risk of amyotrophic lateral sclerosis in Japan. *Neuroepidemiology*. 2009;32:251-256.
62. Monacelli F, Acquarone E, Giannotti C, Borghi R, Nencioni A. Vitamin C, aging and Alzheimer's disease. *Nutrients*. 2017;9: <https://doi.org/10.3390/nu9070670>
63. Kocot J, Luchowska-Kocot D, Kielczykowska M, Musik I, Kurzepa J. Does vitamin C influence neurodegenerative diseases and psychiatric disorders? *Nutrients*. 2017;9: <https://doi.org/10.3390/nu9070659>

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